

the U.S. Department of Agriculture for action.

(8) It fails to include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reasons for the non-compliance.

(9) [Reserved]

(10) The applicant fails to submit a complete environmental assessment which addresses each of the items specified in the applicable format under § 25.31 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.24 of this chapter

(c) If an application is determined not to be acceptable for filing, the applicant shall be notified within 30 days of receipt of the application and shall be given the reasons therefore.

(d) If the applicant disputes the findings that his application is not acceptable for filing, he may make written request that the application be filed over protest, in which case it will be filed as of the day originally received.

[40 FR 13825, Mar. 27, 1975, as amended at 50 FR 7517, Feb. 22, 1985; 50 FR 16668, Apr. 26, 1985]

§ 514.111 Refusal to approve an application.

(a) The Commissioner shall, within 180 days after the filing of the application, inform the applicant in writing of his intention to issue a notice of opportunity for a hearing on a proposal to refuse to approve the application, if the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to a new animal drug, that:

(1) The reports of investigations required to be submitted pursuant to section 512(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or

suggested in the proposed labeling thereof; or

(2) The results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; or

(3) The methods used in and the facilities and controls used for the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or

(4) Upon the basis of the information submitted to the Food and Drug Administration as part of the application, or upon the basis of any other information before it with respect to such drug, it has insufficient information to determine whether such drug is safe for use under such conditions. In making this determination the Commissioner shall consider, among other relevant factors:

(i) The probable consumption of such drug and of any substance formed in or on food because of the use of such drug;

(ii) The cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substances;

(iii) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data; and

(iv) Whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice; or

(5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical (field) investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical (field) investigations. They provide the basis for the determination whether there is *substantial evidence* to support the claims of effectiveness for *new animal drugs*.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired;

(ii) Assigns the subjects to test groups in such a way as to minimize bias; and

(iii) Assures comparability in test and control groups of pertinent variables, such as species, age, sex, duration and severity of disease, management practices, and use of drugs other than those being studied. When the effect of such variables is accounted for by an appropriate design, and when, within the same animal, effects due to the test drug can be obtained free of the effects of such variables, the same animal may be used for both the test drug and the control using the controls set forth in paragraph (a)(5)(ii)(a)(4)(i), (ii), or (iii) of this section.

(3) An explanation of the methods of observation and recording of the animal response variable studied and the means of excluding bias or minimizing bias in the observations.

(4) A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of “blinding,” if

used, are to be documented. Generally, four types of comparisons are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated animals.

(ii) Placebo control: Comparison of the results of use of the new animal drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(iii) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the well-being of the animals.

(iv) Historical control: In some circumstances involving diseases with high and predictable mortality (leukemia or tetanus) or with signs and symptoms of predictable duration or severity (some forms of parasitism, bovine hypocalcemia, canine eclampsia) or in the case of prophylaxis where morbidity is predictable, the results of use of a new animal drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable animals with no treatments or with a regimen (therapeutic, diagnostic, prophylactic) whose effectiveness is established.

(5) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

(6) Any of the criteria in this paragraph (a)(5)(ii) may be waived in whole or in part, either before the investigation or in the evaluation of a completed study, by the Director of the Center for Veterinary Medicine with respect to a specific clinical (field) investigation. A petition for such a waiver may be filed by any person who would be adversely affected by application of the criteria to a particular clinical investigation. The petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be or have been followed, the

results of which will yield or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical (field) investigation, what alternative procedures, if any, are to be or have been employed, what results have been obtained, and the basis on which it can be or has been concluded that the clinical (field) investigation will yield or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(b) Standardized test drug: For such an investigation to be considered adequate for consideration for approval of a new animal drug, the test drug must be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(c) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Failure to include an appropriate proposed tolerance for residues in edible products derived from animals or a withdrawal period or other restrictions for use of such drug if any tolerance or withdrawal period or other restrictions for use are required in order to assure that the edible products derived from animals treated with such drug will be safe.

(7) Based on a fair evaluation of all material facts, the labeling is false or misleading in any particular; or

(8) Such drug induces cancer when ingested by man or animal or, after appropriate tests for evaluation of the safety of such drug, induces cancer in man or animal, except that this subparagraph shall not apply with respect to such drug if the Commissioner finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice:

(i) Such drug will not adversely affect the animal for which it is intended; and

(ii) No residue of such drug will be found (by methods of examination prescribed or approved by the Commissioner by regulations) in any edible portion of such animal after slaughter or in any food yielded by, or derived from the living animals.

(9) The applicant fails to submit an adequate environmental assessment under § 25.31 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.24 of this chapter.

(10) The drug fails to satisfy the requirements of subpart E of part 500 of this chapter.

(11) Any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(b) The Commissioner shall within 90 days after the filing of the application inform the applicant in writing of his intention to issue a notice of opportunity for a hearing on a proposal to refuse to approve the application, if the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to an animal feed bearing or containing a new animal drug that:

(1) There is not in effect a regulation established pursuant to section 512(i) of the act (identified in such application)

on the basis of which such application may be approved; or

(2) Such animal feed (including the proposed use of any new animal drug therein or thereon) does not conform to an applicable regulation published pursuant to section 512(i) of the act (identified in such application), or that the purposes or conditions or indications of use prescribed, recommended, or suggested in the labeling of such feed do not conform to the applicable purposes and conditions or indications for use (including warnings) published pursuant to section 512(i) of the act or such labeling omits or fails to conform to other applicable information published pursuant to such section; or

(3) The methods used in and the facilities and controls used for the manufacturing, processing, and packaging of such animal feed are not adequate to preserve the identity, strength, quality, and purity of the new animal drug therein; or

(4) Based on a fair evaluation of all the material facts, such labeling is false or misleading in any particular.

(c) The Commissioner, as provided in § 514.200 of this chapter, shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable, unless by the 30th day following the date of issuance of the letter informing the applicant of the intention to issue a notice of opportunity for a hearing the applicant:

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing.

[40 FR 13825, Mar. 27, 1975, as amended at 43 FR 22675, May 26, 1978; 44 FR 16007, Mar. 16, 1979; 50 FR 7517, Feb. 22, 1985; 50 FR 16668, Apr. 26, 1985; 52 FR 49588, Dec. 31, 1987; 54 FR 18280, Apr. 28, 1989]

§ 514.112 Return of applications for animal feeds bearing or containing new animal drugs.

Applications submitted pursuant to § 514.2 will be returned to the applicant if such applications are incomplete or inaccurate or do not contain an identification of the applicable regulation(s). These regulations include those pub-

lished pursuant to section 512(i) of the act, and are found in part 558 of this chapter. In addition, § 510.515 of this chapter may also provide a basis on which approval of the application relies, as required by § 514.2(b)(10). All reasons for the return of the application will be made known to the applicant.

[51 FR 7392, Mar. 3, 1986]

§ 514.115 Withdrawal of approval of applications.

(a) The Secretary may suspend approval of an application approved pursuant to section 512(c) or (m)(2) of the act and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing on a finding that there is an imminent hazard to the health of man or of the animals for which such new animal drug or animal feed is intended.

(b) The Commissioner shall notify in writing the person holding an application approved pursuant to section 512(c) or (m)(2) of the act and afford an opportunity for a hearing on a proposal to withdraw approval of such application if he finds:

(1) That the application contains any untrue statement of a material fact; or

(2) That the applicant has made any changes from the standpoint of safety or effectiveness beyond the variations provided for in the application unless he has supplemented the application by filing with the Secretary adequate information respecting all such changes and unless there is in effect an approval of the supplemental application, or such changes are those for which written authorization or approval is not required as provided for in § 514.8. The supplemental application shall be treated in the same manner as the original application.

(3) That in the case of an application for use of a new animal drug approved or deemed approved pursuant to section 512(c) of the act:

(i) Experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; or

(ii) New evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods,